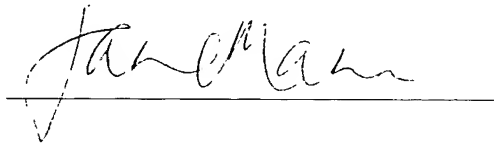
DECLARATION

I, Jane Roberta Mann, B.A., a Translator, of Frank B. Dehn & Co., 59 St Aldates, Oxford OX1 1ST, England, do declare that I have a competent knowledge of the English and German languages and that the document that is annexed hereto is a true and accurate translation of the German text of the U.S. Provisional Application Serial No. 60/429,173 filed November 26, 2002.

I further declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true.

I acknowledge that wilful false statements and the like are punishable by fine or imprisonment, or both [18 U.S.C. 1001] and may jeopardize the validity of the application or any patent issuing therefrom.



Signed this 14th day of October, 2003

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Xanthine derivatives, the preparation thereof and their use as pharmaceutical compositions

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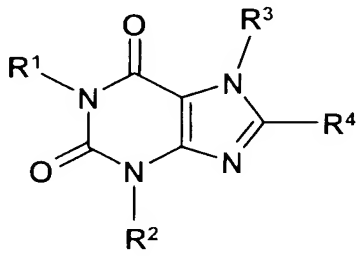
The present invention relates to new substituted xanthines of general formula



(I),

the tautomers, enantiomers, diastereomers, the mixtures thereof, the prodrugs thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV), the preparation thereof, the use thereof for the prevention or treatment of diseases or conditions associated with an increased DPP-IV activity or capable of being prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus, the pharmaceutical compositions containing a compound of general formula (I) or a physiologically acceptable salt thereof as well as processes for the preparation thereof.

The present invention thus relates to the above compounds of general formula I which have valuable pharmacological properties, the pharmaceutical compositions containing the pharmacologically effective compounds, the use thereof and processes for the preparation thereof.

In the above general formula I

R^1 denotes a C_{1-3}-alkyl group substituted by a group R_a, while

R_a denotes a 1,4-dihydro-quinazolinyl or 3,4-dihydro-quinazolinyl group wherein in each case in the benzo moiety

one to three methyne groups may be replaced by nitrogen atoms,

a 3,4-dihydro-isoquinolinyl, 1*H*-benzo[*d*][1,2]oxazinyl, 4*H*-benzo[*e*][1,3]oxazinyl, 4*H*-benzo[*d*][1,3]oxazinyl or 2*H*-benzo[1,4]oxazinyl group, wherein in each case

in the benzo moiety one to three methyne groups may be replaced by nitrogen atoms and in the heterocyclyl moiety a methylene group may be replaced by a carbonyl group,

a 4*H*-benzo[*e*][1,3]thiazinyl, 4*H*-benzo[*d*][1,3]thiazinyl or 2*H*-benzo[1,4]thiazinyl group, wherein in each case

in the benzo moiety one to three methyne groups may be replaced by nitrogen atoms and in the heterocyclyl moiety a methylene group may be replaced by a carbonyl group and a sulphur atom may be replaced by a sulphinyl or sulphonyl group,

a 2-oxo-2*H*-benzo[*e*][1,3]oxazinyl or 2,2-dioxo-1*H*-benzo[*c*][1,2]thiazinyl group, wherein in each case in the benzo moiety

one to three methyne groups may be replaced by nitrogen atoms,

a 2,3-dihydro-1*H*-benzo[*e*][1,4]diazepinyl, 4,5-dihydro-3*H*-benzo[*b*]-[1,4]diazepinyl or 5-oxo-4,5-dihydro-3*H*-benzo[*e*][1,4]diazepinyl group, wherein in each case

in the benzo moiety one to three methyne groups may be replaced by nitrogen atoms and in the heterocyclyl moiety a methylene group may be replaced by a carbonyl group ,

a 2,3-dihydro-benzo[*f*][1,4]oxazepinyl or 2,3-dihydro-benzo[*b*][1,4]oxazepinyl group wherein in each case

in the benzo moiety one to three methyne groups may be replaced by nitrogen atoms and in the heterocyclyl moiety a methylene group may be replaced by a carbonyl group,

a 2,3-dihydro-benzo[*f*][1,4]thiazepinyl or 2,3-dihydro-benzo[*b*][1,4]thiazepinyl group, wherein in each case

in the benzo moiety one to three methyne groups may be replaced by nitrogen atoms and in the heterocyclyl moiety a methylene group may be replaced by a carbonyl group and a sulphur atom may be replaced by a sulphinyl or sulphonyl group,

a 5-oxo-4,5-dihydro-benzo[*f*][1,3,4]oxadiazepinyl group wherein in the benzo moiety

one to three methyne groups may be replaced by nitrogen atoms,

an 11*H*-dibenzo[*b*,*e*]azepinyl or 5H-dibenzo[*a*,*d*]cycloheptenyl group, wherein in each case

in the benzo moiety one to three methyne groups may be replaced by nitrogen atoms and the methylene group in the heterocyclyl moiety may be replaced by an oxygen or sulphur atom, a carbonyl, sulphinyl, sulphonyl or an imino group substituted by R_x, where

R_x denotes a hydrogen atom or a C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkyl, aryl, aryl-C_{1-3}-alkyl, hydroxy-C_{2-4}-alkyl, C_{1-3}-alkyloxy-C_{2-4}-alkyl, C_{3-6}-cycloalkyloxy-C_{2-4}-alkyl, amino-C_{2-4}-alkyl, C_{1-3}-alkylamino-C_{2-4}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{2-4}-alkyl, C_{1-3}-alkyl-carbonyl, C_{1-3}-alkyloxy-carbonyl, C_{1-3}-alkyloxy-carbonyl-C_{1-3}-alkyl, aryl-carbonyl, C_{1-3}-alkyl-sulphonyl or aryl-sulphonyl group,

or a phenanthridinyl, 1,2,3,4-tetrahydro-phenanthridinyl, 5*H*-dibenzo[*d*,*f*][1,3]diazepinyl, 5H-benzo[*e*]pyrrolo[1,2-a][1,4]diazepinyl, thieno[3,2-b][1,4]benzoxazepinyl or a 3-oxo-2,3-dihydro-isoindol-1-ylidene group, wherein in each case

in the benzo moiety one to three methyne groups may be replaced by nitrogen atoms,

while the above-mentioned groups R_a may be substituted by the groups R^{10} to R^{13} and may additionally be substituted by a C_{1-3}-alkyl group and

R^{10} denotes a hydrogen atom,

a fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl, hydroxy, or C_{1-4}-alkyloxy group,

a nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)amino, cyano-C_{1-3}-alkylamino, [N-(cyano-C_{1-3}-alkyl)-N-C_{1-3}-alkyl-amino], C_{1-3}-alkyloxy-carbonyl-C_{1-3}-alkylamino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, or 4-(C_{1-3}-alkyl)-piperazin-1-yl group,

a C_{1-3}-alkyl-carbonylamino, arylcarbonylamino, aryl-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkyloxy-carbonylamino, aminocarbonylamino, C_{1-3}-alkyl-aminocarbonylamino, di-(C_{1-3}-alkyl)aminocarbonylamino, pyrrolidin-1-yl-carbonylamino, piperidin-1-yl-carbonylamino, morpholin-4-yl-carbonylamino, piperazin-1-yl-carbonylamino or 4-(C_{1-3}-alkyl)-piperazin-1-yl-carbonylamino, C_{1-3}-alkyl-sulphonylamino, bis-(C_{1-3}-alkylsulphonyl)-amino, aminosulphonylamino, C_{1-3}-alkylamino-sulphonylamino, di-(C_{1-3}-alkyl)amino-sulphonylamino, pyrrolidin-1-yl-sulphonylamino, piperidin-1-yl-sulphonylamino, morpholin-4-yl-sulphonylamino, piperazin-1-yl-sulphonylamino or 4-(C_{1-3}-alkyl)-piperazin-1-yl-sulphonylamino, (C_{1-3}-alkylamino)thiocarbonylamino, (C_{1-3}-alkyloxy-carbonylamino)-carbonylamino, arylsulphonylamino or aryl-C_{1-3}-alkyl-sulphonylamino group,

an N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino, N-(C_{1-3}-alkyl)-aryl-C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyloxy-carbonylamino, N-(aminocarbonyl)-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl-aminocarbonyl)-C_{1-3}-alkylamino , N-[di-(C_{1-3}-alkyl)aminocarbonyl]-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-sulphonylamino, N-(C_{1-3}-alkyl)-arylsulphonylamino or N-(C_{1-3}-alkyl)-aryl-C_{1-3}-alkyl-sulphonylamino group,

a 2-oxo-imidazolidin-1-yl, 2,4-dioxo-imidazolidin-1-yl, 2,5-dioxo-imidazolidin-1-yl or 2-oxo-hexahydropyrimidin-1-yl group wherein the nitrogen atom in the 3 position may be substituted in each case by a methyl or ethyl group,

a cyano, carboxy, C_{1-3}-alkyloxy-carbonyl, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl or 4-(C_{1-3}-alkyl)-piperazin-1-yl-carbonyl group,

a C_{1-3}-alkyl-carbonyl or an arylcarbonyl group,

a carboxy-C_{1-3}-alkyl, C_{1-3}-alkyloxy-carbonyl-C_{1-3}-alkyl, cyano-C_{1-3}-alkyl, aminocarbonyl-C_{1-3}-alkyl, C_{1-3}-alkyl-aminocarbonyl-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyl, pyrrolidin-1-yl-carbonyl-C_{1-3}-alkyl, piperidin-1-yl-carbonyl-C_{1-3}-alkyl, morpholin-4-yl-carbonyl-C_{1-3}-alkyl, piperazin-1-yl-carbonyl-C_{1-3}-alkyl or 4-(C_{1-3}-alkyl)-piperazin-1-yl-carbonyl-C_{1-3}-alkyl group,

a carboxy-C_{1-3}-alkyloxy, C_{1-3}-alkyloxy-carbonyl-C_{1-3}-alkyloxy, cyano-C_{1-3}-alkyloxy, aminocarbonyl-C_{1-3}-alkyloxy, C_{1-3}-alkyl-aminocarbonyl-C_{1-3}-alkyloxy, di-(C_{1-3}-alkyl)-aminocarbonyl-C_{1-3}-alkyloxy, pyrrolidin-1-yl-carbonyl-C_{1-3}-alkyloxy, piperidin-1-yl-carbonyl-C_{1-3}-alkyloxy, morpholin-4-yl-carbonyl-C_{1-3}-alkyl-oxy, piperazin-1-yl-carbonyl-C_{1-3}-alkyloxy or 4-(C_{1-3}-alkyl)-piperazin-1-yl-carbonyl-C_{1-3}-alkyloxy group,

a hydroxy-C_{1-3}-alkyl, C_{1-3}-alkyloxy-C_{1-3}-alkyl, amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, pyrrolidin-1-yl-C_{1-3}-alkyl, piperidin-1-yl-C_{1-3}-alkyl, morpholin-4-yl-C_{1-3}-alkyl, piperazin-1-yl-C_{1-3}-alkyl, 4-(C_{1-3}-alkyl)-piperazin-1-yl-C_{1-3}-alkyl group,

a hydroxy-C_{1-3}-alkyloxy, C_{1-3}-alkyloxy-C_{1-3}-alkyloxy, C_{1-3}-alkyl-sulphanyl-C_{1-3}-alkyloxy, C_{1-3}-alkylsulphinyl-C_{1-3}-alkyloxy, C_{1-3}-alkylsulphonyl-C_{1-3}-alkyloxy, amino-C_{1-3}-alkyloxy, C_{1-3}-alkylamino-C_{1-3}-alkyloxy, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyloxy, pyrrolidin-1-yl-C_{1-3}-alkyloxy, piperidin-1-yl-C_{1-3}-alkyloxy, morpholin-4-yl-C_{1-3}-alkyloxy, piperazin-1-yl-C_{1-3}-alkyloxy, 4-(C_{1-3}-alkyl)-piperazin-1-yl-C_{1-3}-alkyloxy group,

a mercapto, C_{1-3}-alkylsulphanyl, C_{1-3}-alkysulphinyl, C_{1-3}-alkylsulphonyl, C_{1-3}-alkylsulphonyloxy, arylsulphonyloxy,

trifluoromethylsulphanyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a sulpho, aminosulphonyl, C_{1-3}-alkyl-aminosulphonyl, di-(C_{1-3}-alkyl)-aminosulphonyl, pyrrolidin-1-yl-sulphonyl, piperidin-1-yl-sulphonyl, morpholin-4-yl-sulphonyl, piperazin-1-yl-sulphonyl or 4-(C_{1-3}-alkyl)-piperazin-1-yl-sulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a C_{2-4}-alkenyl or C_{2-4}-alkynyl group,

a C_{3-4}-alkenyloxy or C_{3-4}-alkynyloxy group,

a C_{3-6}-cycloalkyl or C_{3-6}-cycloalkyloxy group,

a C_{3-6}-cycloalkyl-C_{1-3}-alkyl or C_{3-6}-cycloalkyl-C_{1-3}-alkyloxy group or

an aryl, aryloxy, aryl-C_{1-3}-alkyl or aryl-C_{1-3}-alkyloxy group,

R^{11} and R^{12}, which may be identical or different, in each case denote a hydrogen atom, a fluorine, chlorine, bromine or iodine atom, a C_{1-3}-alkyl, trifluoromethyl, hydroxy or C_{1-3}-alkyloxy group or a cyano group, or

R^{11} together with R^{12}, if they are bound to adjacent carbon atoms, also denote a methylenedioxy, difluoromethylenedioxy, ethylenedioxy or a straight-chain C_{3-5}-alkylene group
and

R^{13} denotes a hydrogen atom, a fluorine, chlorine or bromine atom, a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkyloxy group,

R^2 denotes a hydrogen atom,

a C_{1-6}-alkyl group,

a C_{2-4}-alkenyl group,

a C_{3-4}-alkynyl group,

a C_{3-6}-cycloalkyl group,

a C_{3-6}-cycloalkyl-C_{1-3}-alkyl group,

a tetrahydrofuran-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydrofuranylmethyl or tetrahydropyranylmethyl group,

an aryl group,

an aryl-C_{1-4}-alkyl group,

an aryl-C_{2-3}-alkenyl group,

an arylcarbonyl-C_{1-2}-alkyl group,

a heteroaryl-C_{1-3}-alkyl group,

a furanylcarbonylmethyl, thienylcarbonylmethyl, thiazolylcarbonylmethyl or pyridylcarbonylmethyl group,

a C_{1-4}-alkyl-carbonyl-C_{1-2}-alkyl group,

a C_{3-6}-cycloalkyl-carbonyl-C_{1-2}-alkyl group,

an aryl-A-C_{1-3}-alkyl group, while A denotes an oxygen or sulphur atom, an imino, C_{1-3}-alkylimino, sulphinyl or sulphonyl group,

a C_{1-4}-alkyl group substituted by a group R_b, while

R_b denotes a cyano, carboxy, C_{1-3}-alkyloxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, di-(C_{1-3}-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

or a C_{2-4}-alkyl group substituted by a group R_c, while

R_c denotes a hydroxy, C_{1-3}-alkyloxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl or 4-ethyl-piperazin-1-yl group and is isolated from the cyclic nitrogen atom in the 3 position of the xanthine structure by at least two carbon atoms,

R^3 denotes a C_{3-8}-alkyl group,

a C_{1-3}-alkyl group substituted by a group R_d, while

R_d denotes a C_{3-7}-cycloalkyl group optionally substituted by one or two C_{1-3}-alkyl groups,

a C_{5-7}-cycloalkenyl group optionally substituted by one or two C_{1-3}-alkyl groups,

an aryl group or

a furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl,

pyridyl, pyridazinyl, pyrimidyl or pyrazinyl group, while the above-mentioned heterocyclic groups may be substituted in each case by one or two C_{1-3}-alkyl groups or by a fluorine, chlorine, bromine or iodine atom or by a trifluoromethyl, cyano or C_{1-3}-alkyloxy group,

a C_{3-8}-alkenyl group,

a C_{3-6}-alkenyl group substituted by a fluorine, chlorine or bromine atom or a trifluoromethyl group,

a C_{3-8}-alkynyl group,

an aryl group or

an aryl-C_{2-4}-alkenyl group,

and

R^4 denotes an azetidin-1-yl or pyrrolidin-1-yl group which is substituted in the 3 position by an amino, C_{1-3}-alkylamino or a di-(C_{1-3}-alkyl)amino group and may additionally be substituted by one or two C_{1-3}-alkyl groups,

a piperidin-1-yl or hexahydroazepin-1-yl group which is substituted in the 3 position or in the 4 position by an amino, C_{1-3}-alkylamino or a di-(C_{1-3}-alkyl)amino group and may additionally be substituted by one or two C_{1-3}-alkyl groups,

a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl-moiety is additionally substituted by an aminocarbonyl, C_{1-2}-alkyl-aminocarbonyl, di-(C_{1-2}-alkyl)aminocarbonyl, pyrrolidin-1-yl-carbonyl, (2-cyano-pyrrolidin-1-yl)-carbonyl, thiazolidin-3-yl-carbonyl, (4-cyano-thiazolidin-3-yl)carbonyl, piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl group,

a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl-moiety is additionally substituted in the 4 position or in the 5 position by a hydroxy or methoxy group,

a 3-amino-piperidin-1-yl group wherein the methylene group in 2 position or in 6 position is replaced by a carbonyl group,

a piperidin-1-yl or hexahydroazepin-1-yl group substituted in the 3 position by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, wherein in each case two hydrogen atoms on the carbon skeleton of the piperidin-1-yl or hexahydroazepin-1-yl group are replaced by a straight-chain alkylene bridge, while this bridge contains 2 to 5 carbon atoms, if the two hydrogen atoms are located on the same carbon atom, or contains 1 to 4 carbon atoms if the hydrogen atoms are located on adjacent carbon atoms, or contains 1 to 4 carbon atoms, if the hydrogen atoms are located on carbon atoms which by are separated by one atom, or contains 1 to 3 carbon atoms if the two hydrogen atoms are located on carbon atoms which are separated by two atoms,

an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl or hexahydroazepin-1-yl group which is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a piperazin-1-yl or [1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C_{1-3}-alkyl groups,

a 3-imino-piperazin-1-yl, 3-imino-[1,4]diazepan-1-yl or 5-imino-[1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C_{1-3}-alkyl groups,

a [1,4]diazepan-1-yl group optionally substituted by one or two C_{1-3}-alkyl groups, which is substituted by an amino group in the 6 position,

a C_{3-7}-cycloalkyl group which is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl group which is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, while the two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

an N-(C_{3-7}-cycloalkyl)-N-(C_{1-3}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group, while the two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

a C_{3-7}-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an N-(C_{3-7}-cycloalkyl)-N-(C_{1-3}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an N-(C_{3-7}-cycloalkyl-C_{1-2}-alkyl)-N-(C_{1-2}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkyl-C_{1-2}-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an N-(C_{3-7}-cycloalkyl-C_{1-2}-alkyl)-N-(C_{1-2}-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or a di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

an R^{19}-C_{2-4}-alkylamino group wherein R^{19} is separated from the nitrogen atom of the C_{2-4}-alkylamino moiety by at least two carbon atoms and

R^{19} denotes an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

an R^{19}-C_{2-4}-alkylamino group wherein the nitrogen atom of the C_{2-4}-alkylamino moiety is substituted by a C_{1-3}-alkyl group and R^{19} is separated from the nitrogen atom of the C_{2-4}-alkylamino moiety by at least two carbon atoms, while R^{19} is as hereinbefore defined,

an amino group substituted by the group R^{20} wherein

R^{20} denotes an azetidin-3-yl, azetidin-2-ylmethyl, azetidin-3-ylmethyl, pyrrolidin-3-yl, pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl, piperidin-3-yl, piperidin-4-yl, piperidin-2-ylmethyl, piperidin-3-ylmethyl or piperidin-4-ylmethyl group, while the groups mentioned for R^{20} may each be substituted by one or two C_{1-3}-alkyl groups,

an amino group substituted by the group R^{20} and a C_{1-3}-alkyl group wherein R^{20} is as hereinbefore defined, while the groups mentioned for R^{20} may each be substituted by one or two C_{1-3}-alkyl groups,

a R^{19}-C_{3-4}-alkyl group wherein the C_{3-4}-alkyl moiety is straight-chain and may additionally be substituted by one or two C_{1-3}-alkyl groups, while R^{19} is as hereinbefore defined,

a 3-amino-2-oxo-piperidin-5-yl or 3-amino-2-oxo-1-methyl-piperidin-5-yl group,

a pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, hexahydroazepin-3-yl or hexahydroazepin-4-yl group which is substituted in the 1 position by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)amino group,

or an azetidin-2-yl-C_{1-2}-alkyl, azetidin-3-yl-C_{1-2}-alkyl, pyrrolidin-2-yl-C_{1-2}-alkyl, pyrrolidin-3-yl, pyrrolidin-3-yl-C_{1-2}-alkyl, piperidin-2-yl-C_{1-2}-alkyl, piperidin-3-yl, piperidin-3-yl-C_{1-2}-alkyl, piperidin-4-yl or piperidin-4-yl-C_{1-2}-alkyl group, while the above-mentioned groups may each be substituted by one or two C_{1-3}-alkyl groups,

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, which may be mono- or disubstituted by R_h independently of one another, where the substituents are identical or different and R_h denotes a fluorine, chlorine, bromine or iodine atom, a trifluoromethyl, cyano, nitro, amino, aminocarbonyl, aminosulphonyl, methylsulphonyl, acetylamino, methylsulphonylamino, C_{1-3}-alkyl, cyclopropyl, ethenyl, ethynyl, hydroxy, C_{1-3}-alkyloxy, difluoromethoxy or trifluoromethoxy group,

by the heteroaryl groups mentioned in the definitions of the above mentioned groups are meant a pyrrolyl, furanyl, thienyl, pyridyl, indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl group,

or a pyrrolyl, furanyl, thienyl or pyridyl group wherein one or two methyne groups are replaced by nitrogen atoms,

or an indolyl, benzofuranyl, benzothiophenyl, quinolinyl or isoquinolinyl group wherein one to three methyne groups are replaced by nitrogen atoms,

and the above-mentioned heteroaryl groups may be mono- or disubstituted by R_h, while the substituents may be identical or different and R_h is as hereinbefore defined,

and, unless otherwise specified, the above-mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof, the prodrugs thereof and the salts thereof.

Compounds of the above general formula I which contain one or more groups that can be cleaved *in vivo* are so-called prodrugs.

The carboxy groups mentioned in the definition of the above mentioned groups may be replaced by a group which can be converted into a carboxy group *in vivo* or by a group which is negatively charged under physiological conditions,

and furthermore the amino and imino groups mentioned in the definition of the above mentioned groups may be substituted by a group which can be cleaved *in vivo*. Such groups are described for example in WO 98/46576 and by N.M. Nielsen *et al.* in International Journal of Pharmaceutics 39, 75-85 (1987).

By a group which can be converted *in vivo* into a carboxy group is meant, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol wherein the alcohol moiety is preferably a C_{1-6}-alkanol, a phenyl-C_{1-3}-alkanol, a C_{3-9}-cycloalkanol, while a C_{5-8}-cycloalkanol may additionally be substituted by one or two C_{1-3}-alkyl groups, a C_{5-8}-cycloalkanol wherein a methylene group in the 3 or 4 position is replaced by an oxygen atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl, phenyl-C_{1-3}-alkyloxycarbonyl or C_{2-6}-alkanoyl group and the cycloalkanol moiety may additionally be substituted by one or two C_{1-3}-alkyl groups, a C_{4-7}-cycloalkenol, a C_{3-5}-alkenol, a phenyl-C_{3-5}-alkenol, a C_{3-5}-alkynol or phenyl-C_{3-5}-alkynol with the proviso that no bonds to the oxygen atom start from a carbon atom which

carries a double or triple bond, a C_{3-8}-cycloalkyl-C_{1-3}-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkyl moiety by one or two C_{1-3}-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula

$$R_p\text{-}CO\text{-}O\text{-}(R_qCR_r)\text{-}OH,$$

wherein

R_p denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, C_{1-8}-alkyloxy, C_{5-7}-cycloalkyloxy, phenyl or phenyl-C_{1-3}-alkyl group,

R_q denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_r denotes a hydrogen atom or a C_{1-3}-alkyl group,

by a group which is negatively charged under physiological conditions is meant, for example, a tetrazol-5-yl, phenylcarbonylaminocarbonyl, trifluoromethylcarbonylaminocarbonyl, C_{1-6}-alkylsulphonylamino, phenylsulphonylamino, benzylsulphonylamino, trifluoromethylsulphonylamino, C_{1-6}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, benzylsulphonylaminocarbonyl or perfluoro-C_{1-6}-alkylsulphonylaminocarbonyl group

and by a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as a phenylcarbonyl group optionally mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3}-alkyl or C_{1-3}-alkyloxy groups, while the substituents may be identical or different, a pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group, a C_{1-16}-alkyloxycarbonyl or C_{1-16}-alkylcarbonyloxy group, wherein hydrogen atoms may be wholly or partially replaced by fluorine or chlorine atoms such as the methoxycarbonyl,

ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, methylcarbonyloxy, ethylcarbonyloxy, 2,2,2-trichloroethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy, tert.butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, octylcarbonyloxy, nonylcarbonyloxy, decylcarbonyloxy, undecylcarbonyloxy, dodecylcarbonyloxy or hexadecylcarbonyloxy group, a phenyl-C_{1-6}-alkyloxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a 3-amino-propionyl group wherein the amino group may be mono- or disubstituted by C_{1-6}-alkyl or C_{3-7}-cycloalkyl groups and the substituents may be identical or different, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkyloxycarbonyl, C_{1-3}-alkyloxy-C_{2-4}-alkyloxy-C_{2-4}-alkyloxycarbonyl, R_p-CO-O-(R_qCR_r)-O-CO, C_{1-6}-alkyl-CO-NH-(R_sCR_t)-O-CO or C_{1-6}-alkyl-CO-O-(R_sCR_t)-(R_sCR_t)-O-CO group, wherein R_p to R_r are as hereinbefore defined,

R_s and R_t, which may be identical or different, denote hydrogen atoms or C_{1-3}-alkyl groups.

Moreover, the saturated alkyl and alkyloxy moieties which contain more than 2 carbon atoms mentioned in the foregoing definitions and those that follow, unless otherwise stated, also include the branched isomers thereof such as, for example, the isopropyl, tert.butyl, isobutyl group, etc.

R^2 for example in each case denotes a hydrogen atom, a methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, 2-propen-1-yl, 2-propyn-1-yl, cyclopropylmethyl, benzyl, 2-phenylethyl, phenylcarbonylmethyl, 3-phenylpropyl, 2-hydroxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 2-(pyrrolidino)ethyl, 2-(piperidino)ethyl, 2-(morpholino)ethyl, 2-(piperazino)ethyl, 2-(4-methylpiperazino)ethyl, 3-hydroxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3-(dimethylamino)propyl, 3-(diethylamino)propyl, 3-(pyrrolidino)propyl, 3-(piperidino)propyl, 3-(morpholino)propyl, 3-

(piperazino)propyl, 3-(4-methylpiperazino)propyl, carboxymethyl, (methoxycarbonyl)methyl, (ethoxycarbonyl)methyl, 2-carboxyethyl, 2-(methoxycarbonyl)ethyl, 2-(ethoxycarbonyl)ethyl, 3-carboxypropyl, 3-(methoxycarbonyl)propyl, 3-(ethoxycarbonyl)propyl, (aminocarbonyl)methyl, (methylaminocarbonyl)methyl, (dimethylaminocarbonyl)methyl, (pyrrolidinocarbonyl)methyl, (piperidinocarbonyl)methyl, (morpholinocarbonyl)-methyl, 2-(aminocarbonyl)ethyl, 2-(methylaminocarbonyl)ethyl, 2-(dimethylaminocarbonyl)ethyl, 2-(pyrrolidinocarbonyl)ethyl, 2-(piperidino-carbonyl)ethyl, 2-(morpholinocarbonyl)ethyl, cyanomethyl or 2-cyanoethyl group.

R^3 for example may denote a methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, (2-methylcyclopropyl)methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl-, 2-propen-1-yl, 2-methyl-2-propen-1-yl, 3-phenyl-2-propen-1-yl, 2-buten-1-yl, 4,4,4-trifluoro-2-buten-1-yl, 3-buten-1-yl, 2-chloro-2-buten-1-yl, 2-bromo-2-buten-1-yl, 3-chloro-2-buten-1-yl, 3-bromo-2-buten-1-yl, 2-methyl-2-buten-1-yl, 3-methyl-2-buten-1-yl, 2,3-dimethyl-2-buten-1-yl, 3-trifluoromethyl-2-buten-1-yl, 3-methyl-3-buten-1-yl, 1-cyclopenten-1-ylmethyl, (2-methyl-1-cyclopenten-1-yl)methyl, 1-cyclohexen-1-ylmethyl, 2-(1-cyclopenten-1-yl)ethyl, 2-propyn-1-yl, 2-butyn-1-yl, 3-butyn-1-yl, phenyl, methylphenyl, benzyl, a fluorobenzyl, chlorobenzyl, bromobenzyl, methylbenzyl, methoxybenzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-furanylmethyl, 3-furanylmethyl, 2-thienylmethyl or 3-thienylmethyl group.

R^4 for example may denote a 3-aminopyrrolidin-1-yl, 3-aminopiperidin-1-yl, 3-(methylamino)-piperidin-1-yl, 3-(ethylamino)-piperidin-1-yl, 3-(dimethylamino)-piperidin-1-yl, 3-(diethylamino)-piperidin-1-yl, 3-[(2-hydroxyethyl)amino]-piperidin-1-yl, 3-[N-methyl-N-(2-hydroxyethyl)-amino]-piperidin-1-yl, 3-[(3-hydroxypropyl)amino]-piperidin-1-yl, 3-[N-methyl-N-(3-hydroxypropyl)-amino]-piperidin-1-yl, 3-[(carboxymethyl)amino]-piperidin-1-yl, 3-[(methoxycarbonylmethyl)amino]-piperidin-1-yl,

3-[(ethoxycarbonylmethyl)amino]-piperidin-1-yl, 3-[N-methyl-N-(methoxycarbonylmethyl)-amino]-piperidin-1-yl, 3-[N-methyl-N-(ethoxycarbonylmethyl)-amino]-piperidin-1-yl, 3-[(2-carboxyethyl)amino]-piperidin-1-yl, 3-{[2-(methoxycarbonyl)ethyl]amino}-piperidin-1-yl, 3-{[2-(ethoxycarbonyl)ethyl]amino}-piperidin-1-yl, 3-{N-methyl-N-[2-(methoxycarbonyl)ethyl]-amino}-piperidin-1-yl, 3-{N-methyl-N-[2-(ethoxycarbonyl)ethyl]-amino}-piperidin-1-yl, 3-[(aminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(methylaminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(dimethylaminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(ethylaminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(diethylaminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(pyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(2-cyanopyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(4-cyanothiazolidin-3-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(2-aminocarbonylpyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(2-carboxypyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(2-methoxycarbonylpyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(2-ethoxycarbonylpyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(piperidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(morpholin-4-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-amino-2-methyl-piperidin-1-yl, 3-amino-3-methyl-piperidin-1-yl, 3-amino-4-methyl-piperidin-1-yl, 3-amino-5-methyl-piperidin-1-yl, 3-amino-6-methyl-piperidin-1-yl, 2-amino-8-aza-bicyclo[3.2.1]oct-8-yl, 6-amino-2-aza-bicyclo[2.2.2]oct-2-yl, 4-aminopiperidin-1-yl, 3-amino-hexahydroazepin-1-yl, 4-amino-hexahydroazepin-1-yl, piperazin-1-yl, [1,4]diazepan-1-yl, 3-aminocyclopentyl, 3-aminocyclohexyl, 3-(methylamino)-cyclohexyl, 3-(ethylamino)-cyclohexyl, 3-(dimethylamino)-cyclohexyl, 3-(diethylamino)-cyclohexyl, 4-aminocyclohexyl, (2-aminocyclopropyl)amino, (2-aminocyclobutyl)amino, (3-aminocyclobutyl)amino, (2-aminocyclopentyl)amino, (3-amino-cyclopentyl)amino, (2-aminocyclohexyl)amino or (3-aminocyclohexyl)amino group.

Preferred compounds of the above general formula I are those wherein

R^1 denotes a methyl group substituted by a group R_a, where

R_a denotes a 1,4-dihydro-quinazolinyl or 3,4-dihydro-quinazolinyl group,

a 3,4-dihydro-isoquinolinyl group,

a 1*H*-benzo[*d*][1,2]oxazinyl or 1-oxo-1*H*-benzo[*d*][1,2]oxazinyl group,

a 4*H*-benzo[*e*][1,3]oxazinyl or 4-oxo-4H-benzo[*e*][1,3]oxazinyl group,

a 4*H*-benzo[*d*][1,3]oxazinyl or 4-oxo-4*H*-benzo[*d*][1,3]oxazinyl group,

2*H*-benzo[1,4]oxazinyl or 2-oxo-2*H*-benzo[1,4]oxazinyl group,

a 4*H*-benzo[*e*][1,3]thiazinyl or 4-oxo-4*H*-benzo[*e*][1,3]thiazinyl group,

a 4*H*-benzo[*d*][1,3]thiazinyl or 2*H*-benzo[1,4]thiazinyl group,

a 2-oxo-2*H*-benzo[*e*][1,3]oxazinyl or 2,2-dioxo-1*H*-benzo[*c*][1,2]thiazinyl group,

a 2,3-dihydro-1*H*-benzo[*e*][1,4]diazepinyl or 2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepinyl group,

a 4,5-dihydro-3*H*-benzo[*b*][1,4]diazepinyl or 4-oxo-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepinyl group,

a 5-oxo-4,5-dihydro-3*H*-benzo[*e*][1,4]diazepinyl group,

a 2,3-dihydro-benzo[*f*][1,4]oxazepinyl or 2,3-dihydro-benzo[*b*][1,4]oxazepinyl group,

a 2,3-dihydro-benzo[*f*][1,4]thiazepinyl- 2,3-dihydro-benzo[*b*][1,4]thiazepinyl group,

a 5-oxo-4,5-dihydro-benzo[*f*][1,3,4]oxadiazepinyl group,

an 11*H*-dibenzo[*b*,*e*]azepinyl or 11-oxo-11*H*-dibenzo[*b*,*e*]azepinyl group,

an 11*H*-benzo[*e*]pyrido[3,2-*b*]azepinyl group,

a 5*H*-dibenzo[*b*,*e*][1,4]diazepinyl or dibenzo[*b*,*f*][1,4]oxazepinyl group,

a dibenzo[*b*,*f*][1,4]thiazepinyl, 5-oxo-dibenzo[*b*,*f*][1,4]thiazepinyl or 5,5-dioxo-dibenzo[*b*,*f*][1,4]thiazepinyl group,

5H-dibenzo[*a*,*d*]cycloheptenyl or 5*H*-dibenzo[*b*,*f*]azepinyl group,

a phenanthridinyl, benzo[*c*][1,5]naphthyridinyl or 1,2,3,4-tetrahydro-phenanthridinyl group,

a 5*H*-dibenzo[*d*,*f*][1,3]diazepinyl, 5H-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepinyl or thieno[3,2-b][1,4]benzoxazepinyl group

or a 3-oxo-2,3-dihydro-isoindol-1-ylidene group,

while the benzo groups of the above-mentioned groups R_a are substituted by the groups R^{10} to R^{12} and the alkylene units of the above-mentioned groups R_a may be substituted by one or two C_{1-3}-alkyl or C_{1-3}-alkyloxy-carbonyl groups and the imino groups of the above-mentioned groups R_a may be substituted by a C_{1-3}-alkyl group and

R^{10} denotes a hydrogen atom,

a fluorine, chlorine, bromine or iodine atom,

a C_{1-3}-alkyl or cyclopropyl group,

a hydroxy, C_{1-3}-alkyloxy or cyclopropyloxy group,

a nitro, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)amino group,

a C_{1-3}-alkyl-carbonylamino or C_{1-3}-alkyl-sulphonylamino group,

a cyano, carboxy, C_{1-3}-alkyloxy-carbonyl, aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a mercapto, C_{1-3}-alkylsulphanyl, C_{1-3}-alkysulphinyl or C_{1-3}-alkylsulphonyl or aminosulphonyl group or

a difluoromethyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy group and

R^{11} and R^{12}, which may be identical or different, in each case represent a hydrogen atom, a fluorine, chlorine or bromine atom, a methyl, trifluoromethyl or methoxy group,

R^2 denotes a hydrogen atom or

a C_{1-3}-alkyl group,

R^3 denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group,

a 2-butyn-1-yl group or

a 1-cyclopenten-1-ylmethyl group

and

R^4 denotes a (3-amino-piperidin-1-yl) group,

while, unless otherwise stated, the above-mentioned alkyl groups may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

R^1 denotes a methyl group substituted by a group R_a, where

R_a denotes a 1,4-dihydro-quinazolin-2-yl or 3,4-dihydro-quinazolin-2-yl group,

a 3,4-dihydro-isoquinolin-1-yl group,

a 1*H*-benzo[*d*][1,2]oxazin-4-yl or 1-oxo-1*H*-benzo[*d*][1,2]oxazin-4-yl group,

a 4*H*-benzo[*e*][1,3]oxazin-2-yl or 4-oxo-4H-benzo[*e*][1,3]oxazin-2-yl group,

a 4*H*-benzo[*d*][1,3]oxazin-2-yl or 4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl group,

2*H*-benzo[1,4]oxazin-3-yl or 2-oxo-2*H*-benzo[1,4]oxazin-3-yl group,

a 4*H*-benzo[*e*][1,3]thiazin-2-yl or 4-oxo-4*H*-benzo[*e*][1,3]thiazin-2-yl group,

a 4*H*-benzo[*d*][1,3]thiazin-2-yl or 2*H*-benzo[1,4]thiazin-3-yl group,

a 2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-yl or 2,2-dioxo-1*H*-benzo[*c*][1,2]thiazin-4-yl group,

a 2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl or 2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl group,

a 4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-yl or 4-oxo-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-yl group,

a 5-oxo-4,5-dihydro-3*H*-benzo[*e*][1,4]diazepin-2-yl group,

a 2,3-dihydro-benzo[*f*][1,4]oxazepin-5-yl or 2,3-dihydro-benzo[*b*]-[1,4]oxazepin-4-yl group,

a 2,3-dihydro-benzo[*f*][1,4]thiazepin-5-yl or 2,3-dihydro-benzo[*b*]-[1,4]thiazepin-4-yl group,

a 5-oxo-4,5-dihydro-benzo[*f*][1,3,4]oxadiazepin-2-yl group,

an 11*H*-dibenzo[*b*,*e*]azepin-6-yl or 11-oxo-11*H*-dibenzo[*b*,*e*]azepin-6-yl group,

an 11*H*-benzo[*e*]pyrido[3,2-*b*]azepin-6-yl group

a 5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl or dibenzo[*b*,*f*][1,4]oxazepin-11-yl group,

a dibenzo[*b*,*f*][1,4]thiazepin-11-yl, 5-oxo-dibenzo[*b*,*f*][1,4]thiazepin-11-yl or 5,5-dioxo-dibenzo[*b*,*f*][1,4]thiazepin-11-yl group,

a 5H-dibenzo[*a*,*d*]cyclohepten-10-yl or 5*H*-dibenzo[*b*,*f*]azepin-10-yl group,

a phenanthridin-6-yl, benzo[*c*][1,5]naphthyridin-6-yl or 1,2,3,4-tetrahydro-phenanthridin-6-yl group,

a 5*H*-dibenzo[*d*,*f*][1,3]diazepin-6-yl, 5H-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-11-yl or thieno[3,2-b][1,4]benzoxazepinyl-9-yl group

or a 3-oxo-2,3-dihydro-isoindol-1-ylidene group,

while the benzo groups of the above-mentioned groups R_a are substituted by the groups R^{10} to R^{12} and the alkylene units of the above-mentioned groups R_a may be substituted by one or two methyl- or methoxy-carbonyl groups, and the imino groups of the above-mentioned groups R_a may be substituted by a methyl group and

R^{10} denotes a hydrogen atom,

a fluorine, chlorine, bromine or iodine atom,

a methyl or ethyl group,

a hydroxy, methoxy or ethoxy group or

a difluoromethyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy group and

R^{11} and R^{12}, which may be identical or different, each represent a hydrogen atom, a fluorine, chlorine or bromine atom, a methyl, trifluoromethyl or methoxy group,

R^2 denotes a hydrogen atom or

a methyl, ethyl, propyl or isopropyl group,

R^3 denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group,

a 2-butyn-1-yl group or

a 1-cyclopenten-1-ylmethyl group

and

R^4 denotes a (3-amino-piperidin-1-yl) group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

Most particularly preferred compounds of the above general formula I are those wherein

R^1 denotes a 3-methoxycarbonyl-3-methyl-3,4-dihydro-isoquinolin-1-ylmethyl group,

a 1-methyl-2,2-dioxo-1*H*-benzo[*c*][1,2]thiazin-4-ylmethyl group,

a 2,3-dihydro-benzo[*f*][1,4]oxazepin-5-ylmethyl group,

a 2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-ylmethyl group,

a phenanthridin-6-ylmethyl or 1,2,3,4-tetrahydro-phenanthridin-6-ylmethyl group,

an 11*H*-dibenzo[*b*,*e*]azepin-6-ylmethyl group,

a dibenzo[*b*,*f*][1,4]oxazepin-11-ylmethyl group,

or a 3-oxo-2,3-dihydro-isoindol-1-ylidenemethyl group,

R^2 denotes a methyl group,

R^3 denotes a 2-buten-1-yl, 3-methyl-2-buten-1-yl or 2-butyn-1-yl group

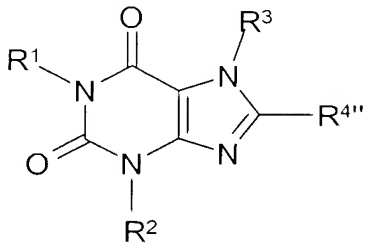
and

R^4 denotes a (3-amino-piperidin-1-yl) group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

According to the invention the compounds of general formula I are obtained by methods known *per se*, for example by the following methods:

a) Deprotecting a compound of general formula



(II),

wherein R^1, R^2 and R^3 are as hereinbefore defined and
$R^{4''}$ denotes one of the groups mentioned for R^4 hereinbefore which contain an imino, amino or alkylamino group, while the imino, amino or alkylamino group is substituted by a protective group.

The liberating of an amino group from a protected precursor is a standard reaction in synthetic organic chemistry. There are many examples of suitable protective groups. A summary of the chemistry of protective groups can be found in Theodora W. Greene and Peter G. M. Wuts, Protective Groups in Organic Synthesis, Second Edition, 1991, published by John Wiley and Sons,

and in Philip J. Kocienski, Protecting Groups, published by Georg Thieme, 1994.

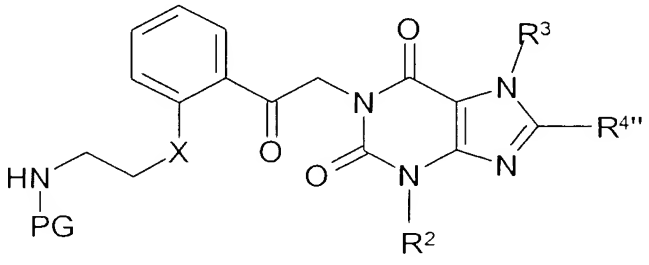
The following are examples of protective groups:

the tert.-butyloxycarbonyl group which can be cleaved by treating with an acid such as for example trifluoroacetic acid or hydrochloric acid or by treating with bromotrimethylsilane or iodotrimethylsilane, optionally using a solvent such as methylene chloride, ethyl acetate, dioxane, methanol, isopropanol or diethylether at temperatures between 0°C and 80°C,

the 2,2,2-trichloroethoxycarbonyl group which can be cleaved by treating with metals such as for example zinc or cadmium in a solvent such as acetic acid or a mixture of tetrahydrofuran and a weak aqueous acid at temperatures between 0°C and the boiling temperature of the solvent used and

the carbobenzyloxycarbonyl group which can be cleaved for example by hydrogenolysis in the presence of a noble metal catalyst such as for example palladium-charcoal and a solvent such as for example alcohols, ethyl acetate, dioxane, tetrahydrofuran or mixtures of these solvents at temperatures between 0°C and the boiling point of the solvent, by treating with boron tribromide in methylene chloride at temperatures between –20°C and ambient temperature, or by treating with aluminium chloride/anisol at temperatures between 0°C and ambient temperature.

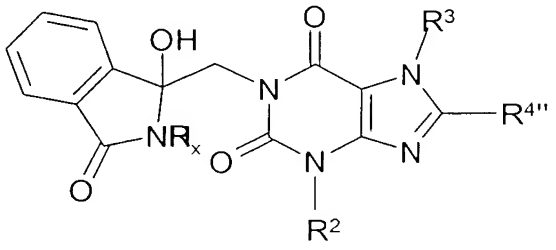
b) Deprotecting and cyclising a compound of general formula



(III),

wherein R^2 and R^3 are as hereinbefore defined,
$R^{4''}$ denotes one of the groups mentioned for R^4 hereinbefore which contain an imino, amino or alkylamino group, while the imino, amino or alkylamino group is substituted by one of the above-mentioned protective groups,
X denotes an oxygen or sulphur atom, a sulphinyl, sulphonyl or an imino group substituted by R_x, and
the $-CH_2-CH_2-X$-phenyl unit is substituted by R^{10} to R^{14} and may additionally be substituted by a C_{1-3}-alkyl group,
while R_x and R^{10} to R^{14} are as hereinbefore defined, and
PG also denotes one of the above-mentioned protective groups,
while the two protective groups may be cleaved simultaneously or one after the other (cf. Example 2).

c) In order to prepare a compound of general formula I wherein R^1 denotes a 3-oxo-2,3-dihydro-isoindol-1-ylidenemethyl group optionally substituted by a group as defined in claims 1 to 4:
Deprotecting and dehydrating a compound of general formula



(IV),

wherein the benzo group is substituted by R^{10} to R^{14},
and R^{10} to R^{14} as well as R_x, R^2 and R^3 are as hereinbefore defined, and
$R^{4''}$ denotes one of the groups mentioned for R^4 hereinbefore which contain an imino, amino or alkylamino group, while the imino, amino or alkylamino group is substituted by one of the above-mentioned protective groups and the dehydration is carried out under the same reaction conditions as the cleaving of the protective group (cf. Example 3).

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms racemic salts or derivatives such as e.g. esters or amides of an optically active substance, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-O-p-toluoyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+)- or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)- or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable

salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae II, III and IV used as starting materials are either known from the literature in some cases or may be obtained by methods known from the literature (cf. Examples I to XV).

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on the enzyme DPP-IV.

The biological properties of the new compounds were investigated as follows:

The ability of the substances and their corresponding salts to inhibit the DPP-IV activity can be demonstrated in a test set-up in which an extract of human colon carcinoma cell line Caco-2 is used as the DPP IV source. The differentiation of the cells in order to induce the DPP-IV expression was carried out as described by Reiher et al. in an article entitled "Increased expression of intestinal cell line Caco-2" , which appeared in Proc. Natl. Acad. Sci. Vol. 90, pages 5757-5761 (1993). The cell extract was obtained from cells solubilised in a buffer (10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% Nonidet-P40, pH 8.0) by centrifuging at 35,000 g for 30 minutes at 4°C (to remove cell debris).

The DPP-IV assay was carried out as follows:

50 µl substrate solution (AFC; AFC is amido-4-trifluoromethylcoumarin), final concentration 100 µM, were placed in black microtitre plates. 20 µl of assay buffer (final concentrations 50 mM Tris HCl pH 7.8, 50 mM NaCl, 1 % DMSO) was pipetted in. The reaction was started by adding 30 µl of solubilised Caco-2 protein (final concentration 0.14 µg of protein per well). The test substances to be investigated were typically added prediluted in 20 µl, and the volume of assay buffer was then reduced accordingly. The reaction was carried out at ambient temperature, incubating for 60 minutes. Then the fluorescence was measured in a Victor 1420 Multilabel Counter, the excitation wavelength being 405 nm and the emission wavelength being 535 nm. Blank readings (corresponding to 0 % activity) were obtained in mixtures without any Caco-2 protein (volume replaced by assay buffer), control values (corresponding to 100 % activity) were obtained in mixtures with no substance added. The potency of the test substances in question, expressed as IC_{50} values, was calculated from dosage/activity curves consisting of 11 measuring points in each case. The following results were obtained:

Compound (Example No.)	DPP IV inhibition IC_{50} [nM]
1	13
1(1)	32
1(2)	6
1(3)	5
1(4)	5
2	6
3	20

The compounds prepared according to the invention are well tolerated, as for example when 10 mg/kg of the compound of Example 1(2) were administered to rats by oral route no changes in the animals' behaviour could be detected.

In view of their ability to inhibit DPP-IV activity, the compounds of general formula I according to the invention and the corresponding pharmaceutically acceptable salts thereof are suitable for treating all those conditions or illnesses which can be influenced by the inhibition of the DPP-IV activity. It is therefore to be expected that the compounds according to the invention will be suitable for the prevention or treatment of diseases or conditions such as type I and type II diabetes mellitus, diabetic complications, metabolic acidosis or ketosis, insulin resistance, dyslipidaemias of various origins, arthritis, atherosclerosis and related diseases, obesity, allograft transplantation and calcitonin-induced osteoporosis. In addition these substances are capable of preventing B-cell degeneration such as e.g. apoptosis or necrosis of pancreatic B-cells. The substances are also suitable for improving or restoring the function of pancreatic cells and also increasing the number and size of pancreatic B-cells. Additionally, and on the basis of the role of the Glucagon-Like Peptides, such as e.g. GLP-1 and GLP-2 and their link with DPP-IV inhibition, it is likely that the compounds according to the invention are suitable for achieving, inter alia, a sedative or anxiety-relieving effect and also of favourably affecting catabolic states after operations or hormonal stress responses or of reducing mortality or morbidity after myocardial infarct. They are also suitable for treating all conditions which are connected with the above mentioned effects and which are mediated by GLP-1 or GLP-2. The compounds according to the invention may also be used as diuretics or antihypertensives and are suitable for preventing and treating acute renal failure. They are also suitable for the prevention and treatment of chronic inflammatory intestinal diseases. It is also expected that DPP-IV inhibitors and hence also the compounds according to the invention may be used to treat infertility or to improve fertility in humans or mammals, particularly when the infertility is connected with insulin resistance or polycystic ovary syndrome. The substances are also suitable for treating deficiencies of growth hormone which are associated with reduced stature.

The compounds according to the invention may also be used in conjunction with other active substances. Therapeutic agents which are suitable for such combinations include, for example, antidiabetics, such as metformin,

sulphonylureas (e.g. glibenclamid, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinedione (e.g. rosiglitazone, pioglitazone), PPAR-gamma agonists (e.g. GI 262570), alpha-glucosidase inhibitors (e.g. acarbose, voglibose), alpha2 antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin-4) or amylin. Also, inhibitors of protein tyrosine phosphatase 1, substances which influence deregulated glucose production in the liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol pyruvate carboxykinase, glycogen synthase kinase or pyruvate dehydrokinase, lipid lowering agents, such as HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid and its derivatives, cholesterol absorption inhibitors such as for example ezetimibe, bile acid-binding substances such as for example cholestyramine, HDL-raising compounds such as for example inhibitors of CETP or regulators of ABC1 or active substances for the treatment of obesity, such as e.g. sibutramine or tetrahydrolipostatin, or $ß_3$-agonists such as SB-418790 or AD-9677.

It is also possible to combine the compounds with drugs for treating high blood pressure such as e.g. AII antagonists or ACE inhibitors, diuretics, ß-blockers, etc., or combinations thereof.

The dosage required to achieve such an effect is expediently, by intravenous route, 1 to 100 mg, preferably 1 to 30 mg, and by oral route 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 a day. For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples that follow are intended to illustrate the invention:

Preparation of the starting compounds:

Example I

1-[(1-methyl-2,2-dioxo-1*H*-benzo[*c*][1,2]thiazin-4-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

A mixture of 260 mg of 3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxy-carbonylamino)-piperidin-1-yl]-xanthine, 185 mg of 4-bromo-methyl-1-methyl-1*H*-benzo[*c*][1,2]thiazine-2,2-dioxide and 550 mg of potassium carbonate in 4 ml N,N-dimethylformamide is stirred for about 40 h at ambient temperature. As no reaction of any note can be detected by thin layer chromatography, the mixture is heated to 60° C for 2 h and then stirred for another 15 h at 50°C until the reaction is virtually complete. Then 30 ml of water are added, the precipitate formed is suction filtered and dried. The crude product is purified by chromatography over a silica gel column with petroleum ether/ethyl acetate (1:1) as eluant.

Yield: 225 mg of (59 % of theory)

R_f value: 0.19 (silica gel, petroleum ether/ethyl acetate = 1:1)

Mass spectrum (ESI^+): m/z = 640 $[M+H]^+$

The following compounds are obtained analogously to Example I:

(1) 1-[(3-methoxycarbonyl-3-methyl-3,4-dihydro-isoquinolin-1-yl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.42 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 95:5)

Mass spectrum (ESI^+): m/z = 632 $[M+H]^+$

(2) 1-[2-(2-methoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine

Mass spectrum (ESI^+): m/z = 445, 447 $[M+H]^+$

(3) 1-[2-(2-ethoxycarbonyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
(carried out in N-methylpyrrolidin-2-one at 60°C)
R_f value: 0.35 (silica gel, methylene chloride/methanol = 20:1)
Mass spectrum (ESI^+): m/z = 623 $[M+H]^+$

(4) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-bromo-xanthine
Mass spectrum (ESI^+): m/z = 462, 464 $[M+H]^+$

(5) 1-[(phenanthridin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.80 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 608 $[M+H]^+$

(6) 1-[(1,2,3,4-tetrahydro-phenanthridin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.55 (silica gel, ethyl acetate/ petroleum ether = 2:1)
Mass spectrum (ESI^+): m/z = 612 $[M+H]^+$

(7) 1-[(11*H*-dibenzo[*b*,*e*]azepin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.40 (silica gel, cyclohexane/ethyl acetate = 1:1)
Mass spectrum (ESI^+): m/z = 622 $[M+H]^+$

(8) 1-[(dibenzo[*b*,*f*][1,4]oxazepin-11-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.70 (silica gel, ethyl acetate/cyclohexane = 3:1)
Mass spectrum (ESI^+): m/z = 624 $[M+H]^+$

Example II

4-Bromo-methyl-1-methyl-1*H*-benzo[*c*][1,2]thiazin-2,2-dioxide

390 mg of 1,4-dimethyl-1*H*-benzo[*c*][1,2]thiazin-2,2-dioxide in 20 ml 1,2-dichloroethane are combined with 332 mg of N-bromosuccinimide and 50 mg

of 2,2'-azodiisobutyronitrile. The yellow solution is refluxed for a total of 10 h and then left to stand for another two days at ambient temperature. The reaction mixture is distributed between water and methylene chloride, the organic phase is washed with water, dried over magnesium sulphate and evaporated down. A yellowish resin is left which is purified through a silica gel column with petroleum ether/ethyl acetate (5:1 to 4:1) as eluant. A mixture of 4-bromo-methyl-1-methyl-1*H*-benzo[*c*][1,2]thiazin-2,2-dioxide and 3-bromo-1,4-dimethyl-1*H*-benzo[*c*][1,2]thiazin-2,2-dioxide is obtained, which is further reacted as it is.
Yield: 190 mg (35 % of theory)
Mass spectrum (ESI^+): m/z = 288, 290 $[M+H]^+$

Example III

3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

A mixture of 20.50 g of 3-methyl-7-(3-methyl-2-buten-1-yl)-8-bromo-xanthine, 13.64 g of 3-tert.-butyloxycarbonylamino-piperidine and 20.27 g of potassium carbonate in 100 ml dimethylsulphoxide is stirred for 4 h at 115°C. Then a further 2.50 g of 3-tert.-butyloxycarbonylamino-piperidine are added and the reaction mixture is stirred for a further 2 h at 115°C. The cooled reaction solution is poured onto 1 l of ice water, the precipitate formed is suction filtered, washed with water and dried.
R_f value: 0.60 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 433 $[M+H]^+$

The following compounds are obtained analogously to Example III:

(1) 3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
melting point: 235-237°C
Mass spectrum (ESI^+): m/z = 417 $[M+H]^+$

(2) 1-[2-(2-hydroxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine

Mass spectrum (ESI^+): m/z = 551 $[M+H]^+$

(3) 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.50 (silica gel, cyclohexane/ethyl acetate = 1:2)
Mass spectrum (ESI^+): m/z = 582 $[M+H]^+$

Example IV

3-methyl-7-(3-methyl-2-buten-1-yl)-8-bromo-xanthine

15.37 ml of Hünig base and 9.98 ml of 3,3-dimethylallylbromide are added to 20.00 g of 3-methyl-8-bromo-xanthine in 200 ml of N,N-dimethylformamide. The reaction mixture is stirred for about half an hour at ambient temperature and then diluted with 500 ml of water. The precipitate formed is suction filtered, washed with water and dried.
Yield: 20.50 g (80 % of theory)
Mass spectrum (ESI^+): m/z = 313, 315 $[M+H]^+$

The following compounds are obtained analogously to Example IV:

(1) 3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine
R_f value: 0.72 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 297, 299 $[M+H]^+$

(2) 3-methyl-7-((E)-2-buten-1-yl)-8-bromo-xanthine
Mass spectrum (ESI^+): m/z = 299, 301 $[M+H]^+$

Example V

Methyl 1-chloromethyl-3-methyl-3,4-dihydro-isoquinolin-3-yl-carboxylate

Prepared from methyl 2-(2-chloro-acetylamino)-2-methyl-3-phenyl-propionate analogously to Das et al., *Indian J. Chem.* **1985**, *24B*, 1302.
R_f value: 0.52 (silica gel, petroleum ether/ethyl acetate = 2:1)
Mass spectrum (ESI^+): m/z = 252, 254 $[M+H]^+$

Example VI

1-(2-{2-[2-(tert.-butyloxycarbonylamino)-ethoxy]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine

187 mg of tert.-butyl 2-bromo-ethyl-carbaminate are added to 400 mg of 1-[2-(2-hydroxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine and 150 mg of potassium carbonate in 6 ml N,N-dimethylformamide and the reaction mixture is stirred overnight at 55°C. Then a further 90 mg of tert.-butyl 2-bromo-ethyl-carbaminate are added. After another eight hours at 55°C the reaction is complete. The cooled reaction mixture is combined with water, the precipitate formed is suction filtered, washed with water and dried.

Yield: 368 mg (73 % of theory)

Mass spectrum (ESI^+): m/z = 694 $[M+H]^+$

Example VII

1-[2-(2-hydroxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine

Prepared by treating 1-[2-(2-methoxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(2-butyn-1-yl)-8-bromo-xanthine with boron tribromide in the presence of 4Å molecular sieve in methylene chloride at 4°C.

Mass spectrum (ESI^+): m/z = 431, 433 $[M+H]^+$

Example VIII

1-[(1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine

A mixture of 250 mg of 1-[2-(2-carboxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine, 404 mg of ammonium carbonate, 135 mg of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate, 57 mg of hydroxybenzotriazole and 59 µl of triethylamine in 3 ml of tetrahydrofuran is

stirred for eight hours at ambient temperature. For working up the reaction mixture is diluted with 30 ml of ethyl acetate and washed with 10 % citric acid solution, 10 % potassium carbonate solution and saturated sodium chloride solution. The organic phase is evaporated down and chromatographed through a silica gel column with methylene chloride/methanol (98:2 to 80:20). The cyclised compound is obtained as the main product.
Yield: 160 mg (64 % of theory)
R_f value: 0.40 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^+): m/z = 594 $[M+H]^+$

Example IX

1-[2-(2-carboxy-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

A mixture of 2.60 g of 1-[2-(2-ethoxycarbonyl-phenyl)-2-oxo-ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine and 8 ml of 3 N sodium hydroxide solution in 25 ml of methanol is stirred for two hours at ambient temperature. For working up the reaction mixture is neutralised with 24 ml of 1 N hydrochloric acid, acidified slightly by the addition of 20 ml of 10 % citric acid solution and extracted with ethyl acetate. The combined extracts are washed with saturated sodium chloride solution, dried over magnesium sulphate and evaporated down.
Yield: 2.00 g (80 % of theory)
R_f value: 0.49 (silica gel, methylene chloride/methanol = 9:1)
Mass spectrum (ESI^-): m/z = 593 $[M-H]^-$

Example X

1-[(2-oxo-2,3-dihydro-1H-benzo[*e*][1,4]diazepin-5-yl)methyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

A mixture of 200 mg of 1-{2-[2-(2-chloro-acetylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine, 5 ml of conc. ammonia, 2 ml of tetrahydrofuran and 2 ml of methanol is stirred at ambient temperature for about a week. Then the dark reaction mixture is added to a pack of 14 g of Extrelut and after 20 minutes washed out thoroughly with methylene chloride. The filtrate is evaporated

down and chromatographed through a silica gel column with ethyl acetate/methanol (10:0 to 8:2) as eluant.

Yield: 95 mg (51 % of theory)

R_f value: 0.25 (silica gel, cyclohexane/ethyl acetate = 2:8)

Example XI

1-{2-[2-(2-chloro-acetylamino)-phenyl]-2-oxo-ethyl}-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

51 µl of bromoacetyl chloride are added to 319 mg of 1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine and 60 µl pyridine in 1 ml methylene chloride. The reaction mixture is stirred for two hours at 35°C and after cooling to ambient temperature, combined with 0.5 M citric acid. The organic phase is separated off and the aqueous phase is extracted with methylene chloride. The combined organic phases are evaporated down and chromatographed through a silica gel column with cyclohexane/ethyl acetate (6:4) as eluant.

Yield: 210 mg (58 % of theory)

R_f value: 0.50 (silica gel, cyclohexane/ethyl acetate/isopropanol = 14:3:3)

Mass spectrum (ESI^+): m/z = 628, 630 $[M+H]^+$

Example XII

1-[2-(2-amino-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

Prepared by reduction of 6.34 g 1-[2-(2-nitro-phenyl)-2-oxo-ethyl]-3-methyl-7-((E)-2-buten-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine with 5.15 g iron powder in a mixture of 260 ml of ethanol, 85 ml of water and 33 ml glacial acetic acid at reflux temperature.

Yield: 5.38 g (90 % of theory)

Mass spectrum (ESI^+): m/z = 552 $[M+H]^+$

Example XIII

6-chloromethyl-1,2,3,4-tetrahydro-phenanthridine-hydrochloride

Prepared by treating 110 mg of 6-hydroxymethyl-1,2,3,4-tetrahydro-phenanthridine with 60 µl of thionyl chloride in 2.5 ml methylene chloride at 0°C to ambient temperature.

Yield: 140 mg (100 % of theory)

R_f value: 0.50 (silica gel, petroleum ether/ethyl acetate = 5:1)

Mass spectrum (ESI^+): m/z = 232, 234 $[M+H]^+$

Example XIV

6-hydroxymethyl-1,2,3,4-tetrahydro-phenanthridine

A solution of 350 mg of ethyl 1,2,3,4-tetrahydro-phenanthridin-6-yl-carboxylate in 10 ml of tetrahydrofuran is added dropwise within five minutes to a suspension of 37 mg of lithium borohydride in 15 ml of tetrahydrofuran, while cooling with an ice bath. Then the ice bath is removed and the reaction mixture is stirred for a further 2.5 hours at ambient temperature. For working up, 2 ml of 1 M citric acid are added to the brown reaction solution while cooling with an ice bath. The mixture is stirred with 100 ml of ethyl acetate and 50 ml of water and adjusted to pH 10 with 4 N sodium hydroxide solution. The organic phase is separated off, washed with water, dried over magnesium sulphate and evaporated down. The flask residue is chromatographed through a silica gel column with ethyl acetate/petroleum ether (1:4 to 1:1) as eluant.

Yield: 120 mg (41 % of theory)

R_f value: 0.40 (silica gel, petroleum ether/ethyl acetate = 2:1)

Mass spectrum (ESI^+): m/z = 214 $[M+H]^+$

Example XV

Ethyl 1,2,3,4-tetrahydro-phenanthridin-6-yl-carboxylate

Analogously to the method described by Gonsalves et al. (*Tetrahedron* **1992**, *48*, 6821) a solution of 3.90 g of ethyl 5,6,7,8-tetrahydro-benzo[1,2,4]triazine-3-carboxylate (Sagi et al., *Heterocycles* **1989**, *29*, 2253) is refluxed in 20 ml

of dioxane. Then 8.22 g anthranilic acid and 7.02 g isoamyl nitrite, in each case dissolved in 20 ml dioxane, are simultaneously added dropwise within 25 minutes using two dropping funnels. The reaction mixture is refluxed for a further 30 minutes. For working up the cooled dark brown reaction solution is diluted with 150 ml diethyl ether, washed with 100 ml of 2 N sodium hydroxide solution and with water, dried over magnesium sulphate and evaporated down. The brown, oily flask residue is chromatographed through a silica gel column with ethyl acetate/petroleum ether (20:80 to 50:50) as eluant. The product obtained is still somewhat contaminated but is further reacted without any further purification.

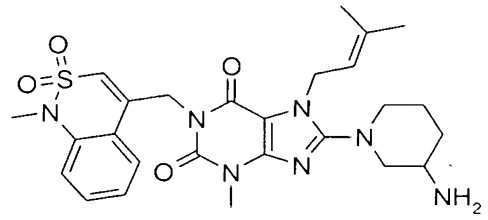
Yield: 380 mg (8 % of theory)

R_f value: 0.55 (silica gel, petroleum ether/ethyl acetate = 2:1)

Mass spectrum (ESI^+): m/z = 256 $[M+H]^+$

Preparation of the final compounds:

Example 1

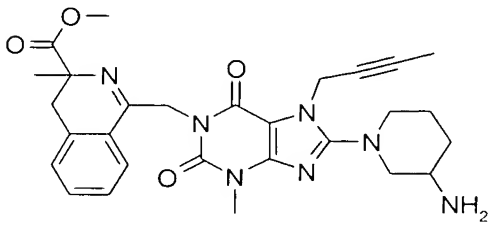


1-[(1-methyl-2,2-dioxo-1*H*-benzo[*c*][1,2]thiazin-4-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

3.5 ml isopropanolic hydrochloric acid (5-6 M) are added to 340 mg of 1-[(1-methyl-2,2-dioxo-1*H*-benzo[*c*][1,2]thiazin-4-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine in 15 ml methylene chloride and the reaction mixture is stirred for three hours at ambient temperature. For working up it is diluted with water and methylene chloride and combined with 18 ml 1N sodium hydroxide solution. The aqueous phase is extracted with methylene chloride and the combined organic phases are washed with water, dried over magnesium sulphate and evaporated down. The yellowish, foamy flask residue is stirred with tert.-butyl-methylether and a little diethyl ether, the light-coloured precipitate formed is suction filtered and dried at 60°C in the drying gun.
Yield: 220 mg (77 % of theory)
melting point: 205-208°C (decomposition)
Mass spectrum (ESI^+): m/z = 540 $[M+H]^+$

The following compounds are obtained analogously to Example 1:

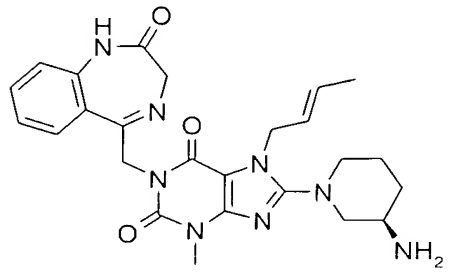
(1) 1-[(3-methoxycarbonyl-3-methyl-3,4-dihydro-isoquinolin-1-yl]methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine



R_f value: 0.42 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI^+): m/z = 532 $[M+H]^+$

(2) 1-[(2-oxo-2,3-dihydro-1H-benzo[*e*][1,4]diazepin-5-yl)methyl]-3-methyl-7-((E)-2-buten-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

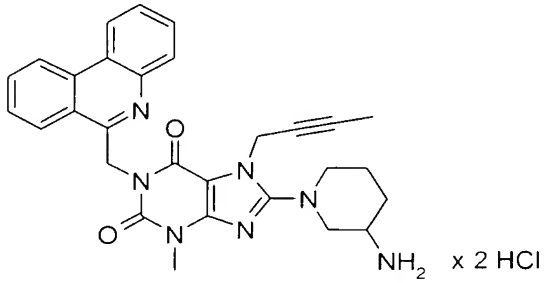


(carried out with trifluoroacetic acid in methylene chloride)

R_f value: 0.50 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:0.1)

Mass spectrum (ESI^+): m/z = 491 $[M+H]^+$

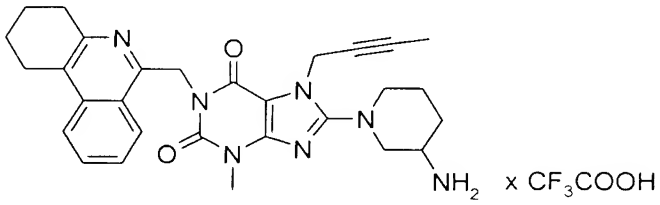
(3) 1-[(phenanthridin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine-dihydrochloride



R_f value: 0.55 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)

Mass spectrum (ESI^+): m/z = 508 $[M+H]^+$

(4) 1-[(1,2,3,4-tetrahydro-phenanthridin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine x trifluoroacetic acid

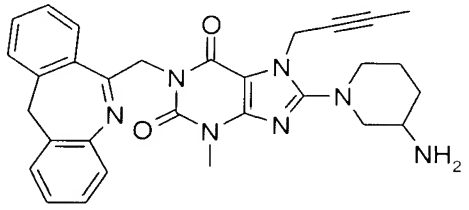


(carried out with trifluoroacetic acid in methylene chloride)

R_f value: 0.75 (aluminium oxide, methylene chloride/methanol = 10:1)

Mass spectrum (ESI^+): m/z = 512 $[M+H]^+$

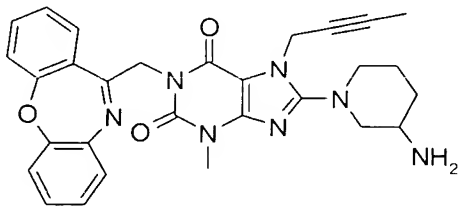
(5) 1-[(11*H*-dibenzo[*b*,*e*]azepin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine



R_f value: 0.45 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)

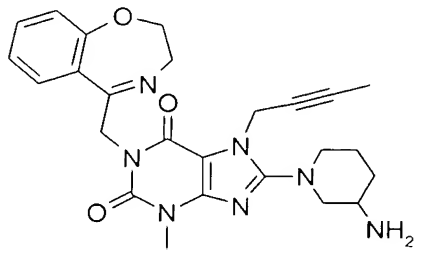
Mass spectrum (ESI^+): m/z = 522 $[M+H]^+$

(6) 1-[(dibenzo[*b*,*f*][1,4]oxazepin-11-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine



Mass spectrum (ESI^+): m/z = 524 $[M+H]^+$

Example 2



1-[(2,3-dihydro-benzo[*f*][1,4]oxazepin-5-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

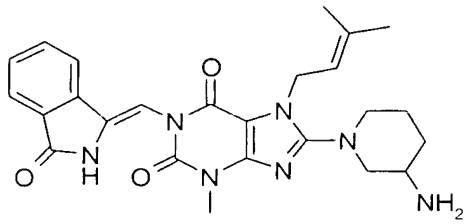
1.15 ml trifluoroacetic acid are added to 368 mg of 1-(2-{2-[2-(tert.-butyloxycarbonylamino)-ethoxy]-phenyl}-2-oxo-ethyl)-3-methyl-7-(2-butyn-1-yl)-8-[3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine in 7 ml methylene chloride while cooling with an ice bath. The reaction mixture is stirred for about three hours at ambient temperature and then added to cooled potassium carbonate solution. The organic phase is washed with saturated sodium chloride solution, dried over magnesium sulphate and evaporated down. The crude product is purified through a silica gel column with methylene chloride/methanol (10:0 to 7:3) as eluant.

Yield: 75 mg (30 % of theory)

R_f value: 0.20 (silica gel, methylene chloride/methanol = 9:1)

Mass spectrum (ESI^+): m/z = 476 $[M+H]^+$

Example 3



1-[(3-oxo-2,3-dihydro-isoindol-1-ylidene)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

150 mg of 1-[(1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-

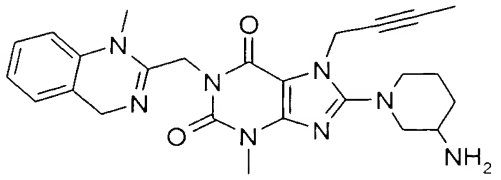
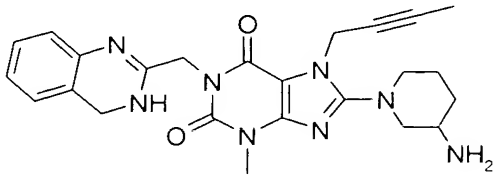
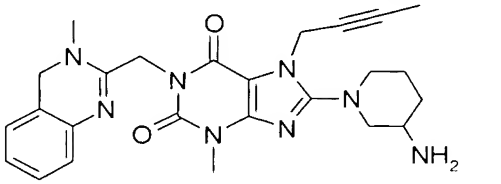
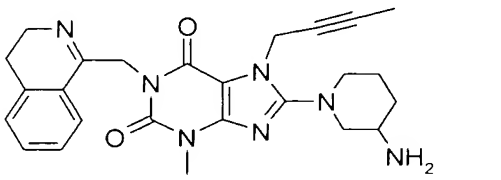
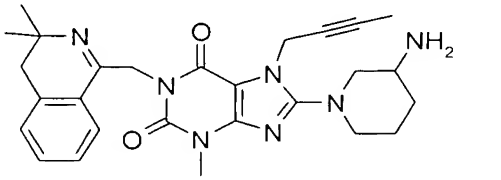
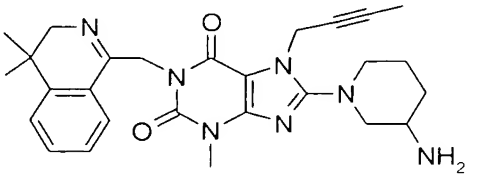
xanthine are stirred for four hours in a mixture of 0.4 ml trifluoroacetic acid and 1.2 ml methylene chloride. For working up the reaction mixture is diluted with 30 ml methylene chloride, combined with 10 ml 10 % potassium carbonate solution and stirred vigorously. The organic phase is separated off, dried over magnesium sulphate and evaporated down.

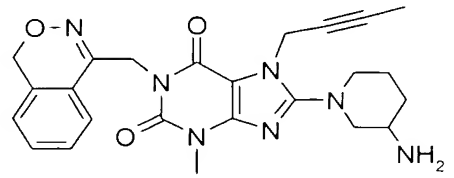
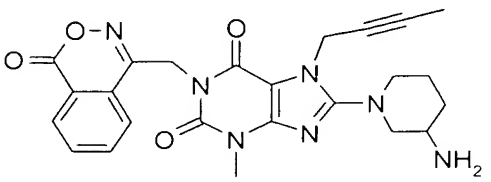
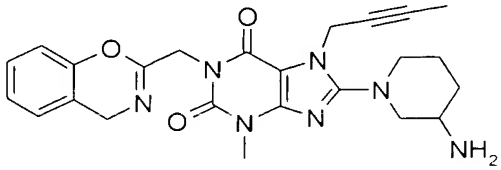
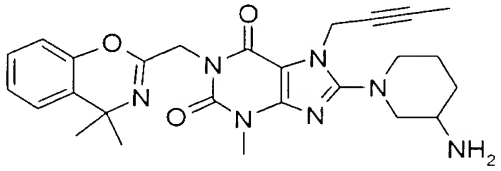
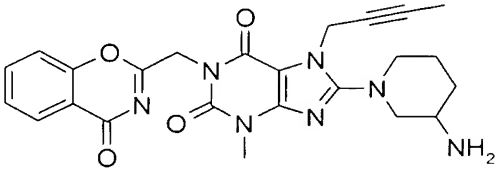
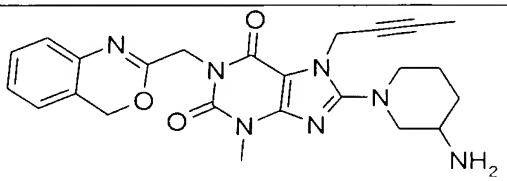
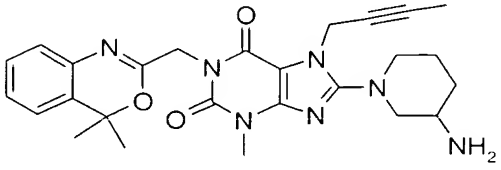
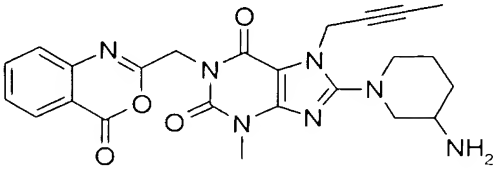
Yield: 50 mg (42 % of theory)

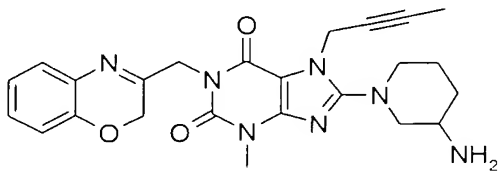
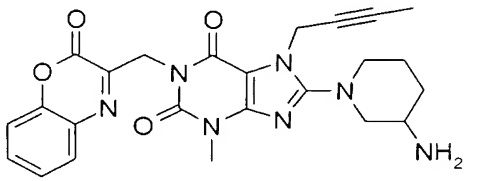
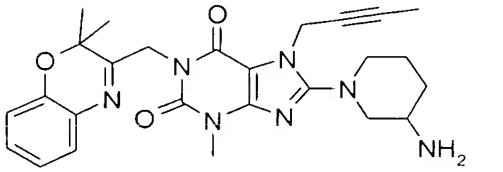
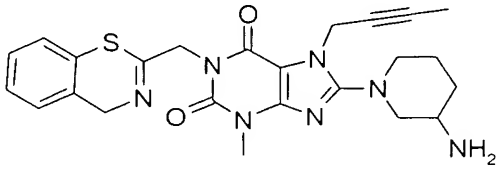
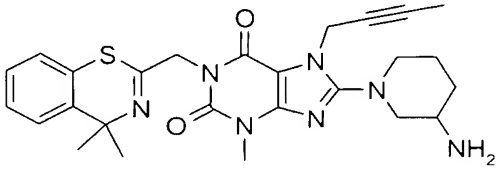
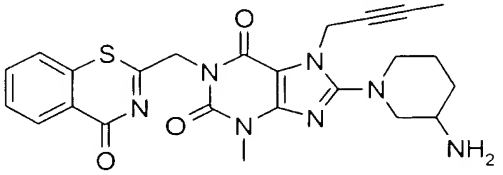
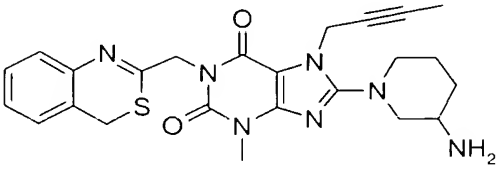
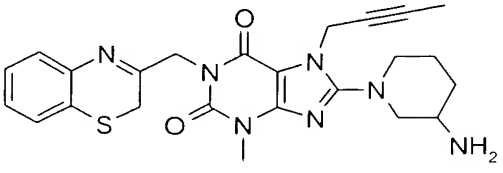
R_f value: 0.56 (Reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)

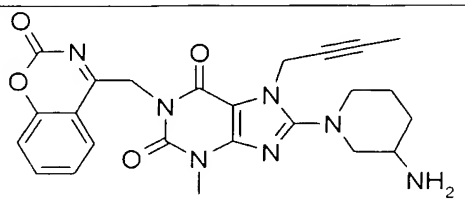
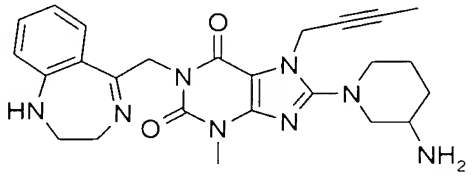
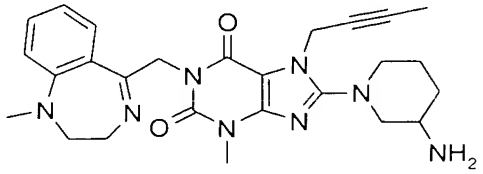
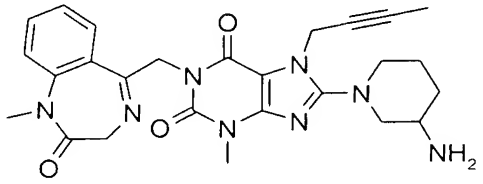
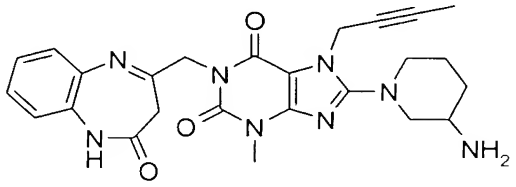
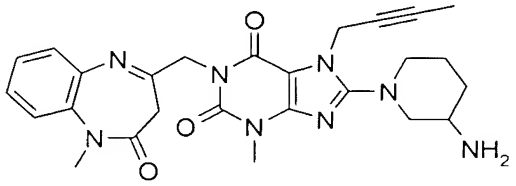
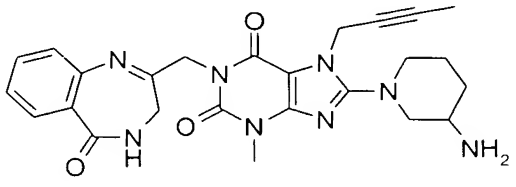
Mass spectrum (ESI^+): m/z = 476 $[M+H]^+$

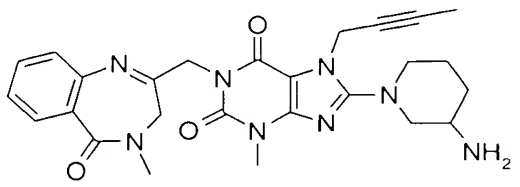
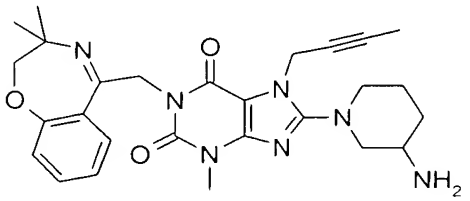
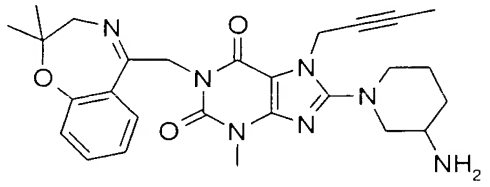
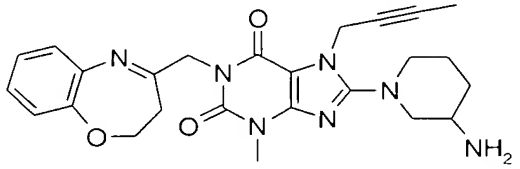
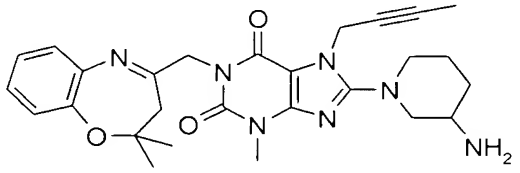
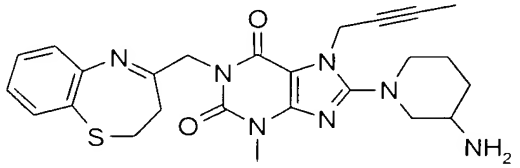
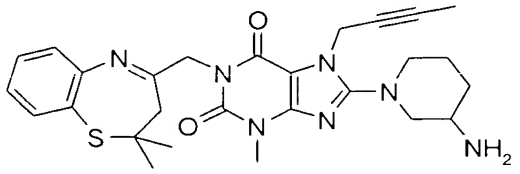
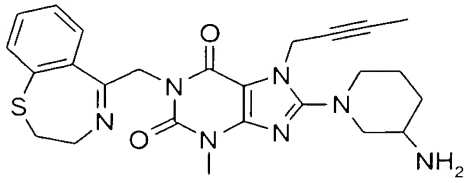
The following compounds may also be obtained analogously to the foregoing Examples and other methods known from the literature:

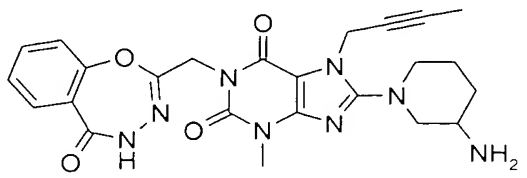
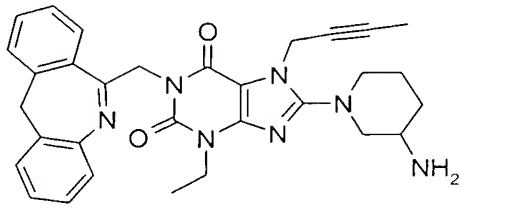
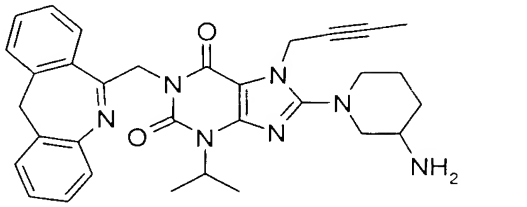
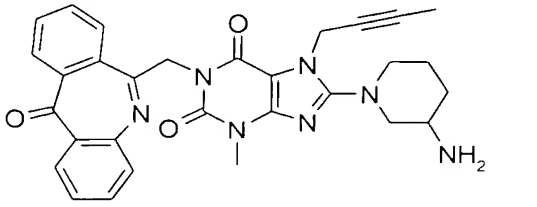
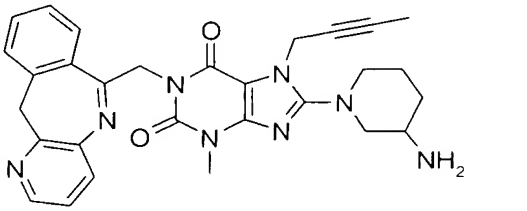
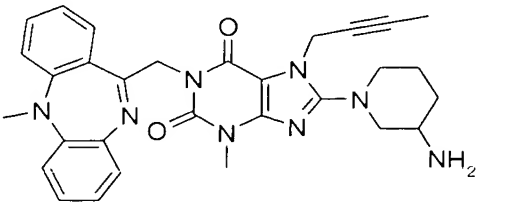
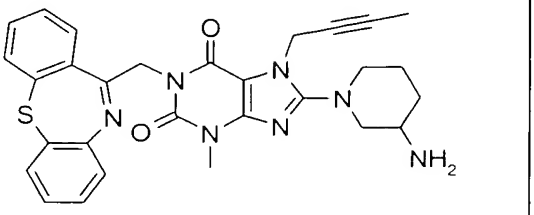
No.	Name	Structural formula
(1)	1-[(1-methyl-1,4-dihydro-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(2)	1-[(3,4-dihydro-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(3)	1-[(3-methyl-3,4-dihydro-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(4)	1-[(3,4-dihydro-isoquinolin-1-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(5)	1-[(3,3-dimethyl-3,4-dihydro-isoquinolin-1-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(6)	1-[(4,4-dimethyl-3,4-dihydro-isoquinolin-1-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	

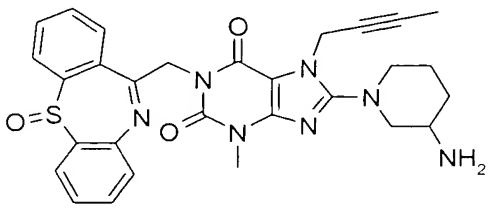
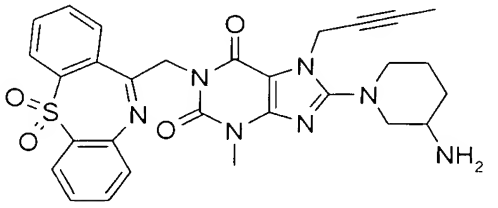
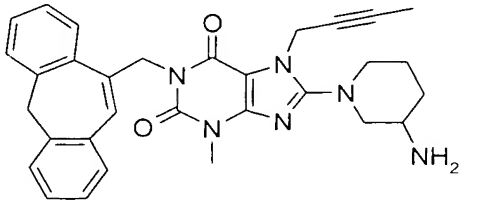
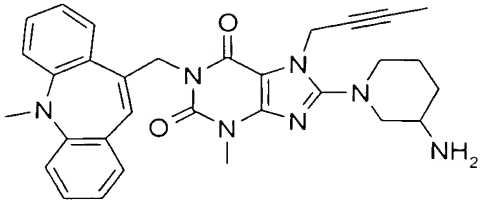
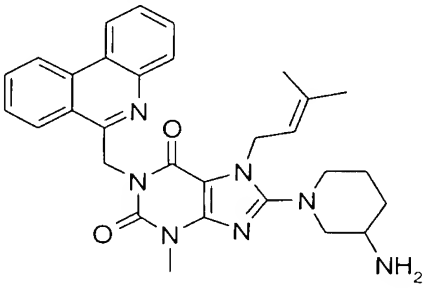
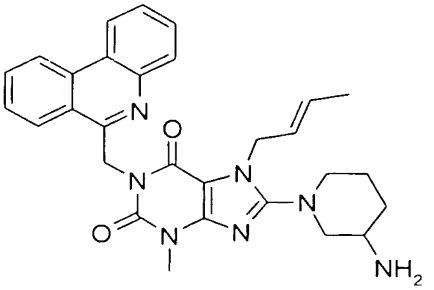
(7)	1-[(1*H*-benzo[*d*][1,2]oxazin-4-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(8)	1-[(1-oxo-1*H*-benzo[*d*][1,2]oxazin-4-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(9)	1-[(4*H*-benzo[*e*][1,3]oxazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(10)	1-[(4,4-dimethyl-4*H*-benzo[*e*][1,3]oxazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(11)	1-[(4-oxo-4*H*-benzo[*e*][1,3]oxazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(12)	1-[(4*H*-benzo[*d*][1,3]oxazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(13)	1-[(4,4-dimethyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(14)	1-[(4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	

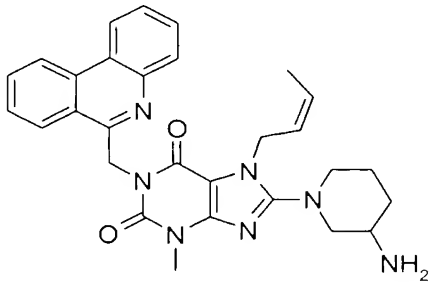
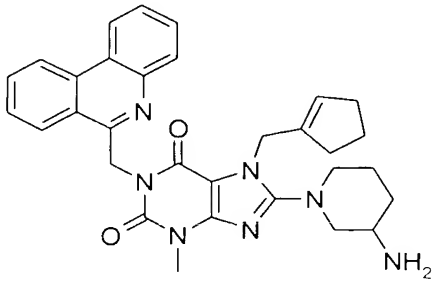
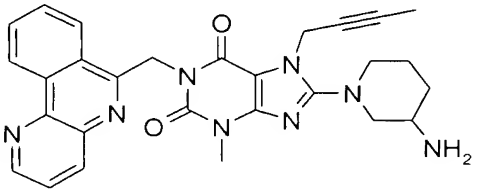
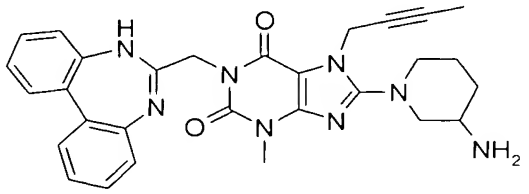
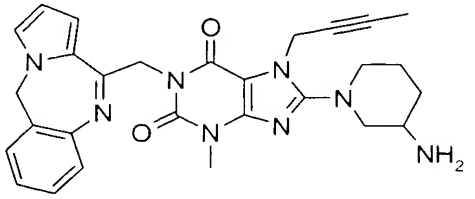
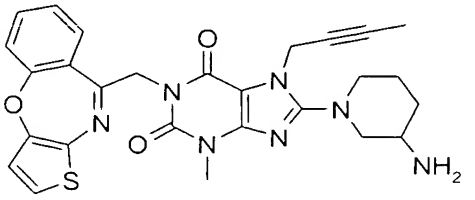
(15)	1-[(2*H*-benzo[1,4]oxazin-3-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(16)	1-[(2-oxo-2*H*-benzo[1,4]oxazin-3-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(17)	1-[(2,2-dimethyl-2*H*-benzo[1,4]oxazin-3-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(18)	1-[4*H*-benzo[*e*][1,3]thiazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(19)	1-[4,4-dimethyl-4*H*-benzo[*e*][1,3]thiazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(20)	1-[4-oxo-4*H*-benzo[*e*][1,3]thiazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(21)	1-[(4*H*-benzo[*d*][1,3]thiazin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(22)	1-[(2*H*-benzo[1,4]thiazin-3-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	

(23)	1-[(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(24)	1-[(2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(25)	1-[(1-methyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(26)	1-[(1-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-5-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(27)	1-[(4-oxo-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(28)	1-[(5-methyl-4-oxo-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(29)	1-[5-oxo-4,5-dihydro-3*H*-benzo[*e*][1,4]diazepin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	

(30)	1-[4-methyl-5-oxo-4,5-dihydro-3*H*-benzo[*e*][1,4]diazepin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(31)	1-[(3,3-dimethyl-2,3-dihydro-benzo[*f*][1,4]oxazepin-5-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(32)	1-[(2,2-dimethyl-2,3-dihydro-benzo[*f*][1,4]oxazepin-5-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(33)	1-[(2,3-dihydro-benzo[*b*][1,4]oxazepin-4-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(34)	1-[(6,6-dimethyl-2,3-dihydro-benzo[*b*][1,4]oxazepin-4-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(35)	1-[(2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(36)	1-[(2,2-dimethyl-2,3-dihydro-benzo[*b*][1,4]thiazepin-4-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(37)	1-[(2,3-dihydro-benzo[*f*][1,4]thiazepin-5-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	

(38)	1-[(5-oxo-4,5-dihydro-benzo[*f*][1,3,4]oxadiazepin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(39)	1-[(11*H*-dibenzo[*b*,*e*]azepin-6-yl)methyl]-3-ethyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(40)	1-[(11*H*-dibenzo[*b*,*e*]azepin-6-yl)methyl]-3-isopropyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(41)	1-[(11-oxo-11*H*-dibenzo[*b*,*e*]azepin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(42)	1-[(11*H*-benzo[*e*]pyrido[3,2-b]azepin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(43)	1-[(5-methyl-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(44)	1-[(dibenzo[*b*,*f*][1,4]thiazepin-11-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	

(45)	1-[(5-oxo-dibenzo[*b*,*f*][1,4]thiazepin-11-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(46)	1-[(5,5-dioxo-dibenzo[*b*,*f*][1,4]thiazepin-11-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(47)	1-[(5*H*-dibenzo[*a*,*d*]cycloheptен-10-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(48)	1-[(5-methyl-5*H*-dibenzo[*b*,*f*]azepin-10-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(49)	1-[(phenanthridin-6-yl)methyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(50)	1-[(phenanthridin-6-yl)methyl]-3-methyl-7-((E)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	

(51)	1-[(phenanthridin-6-yl)methyl]-3-methyl-7-((Z)-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(52)	1-[(phenanthridin-6-yl)methyl]-3-methyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine	
(53)	1-[(benzo[*c*][1,5]naphthyridin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(54)	1-[(5*H*-dibenzo[*d*,*f*][1,3]diazepin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(55)	1-[(5*H*-benzo[*e*]pyrrolo[1,2-a][1,4]diazepin-11-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	
(56)	1-[(thieno[3,2-b][1,4]benzoxazepin-9-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine	

Example 4

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 5

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example 6

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example 7

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance		150.0 mg
corn starch (dried)	approx.	80.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		3.0 mg
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 8

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 9

Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g
dist. water ad	100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol

solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 10

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 11

Ampoules containing 50 mg of active substance

Composition:

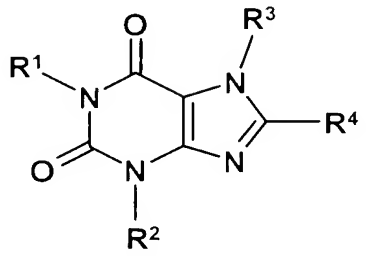
active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Abstract

The present invention relates to substituted xanthines of general formula



(I),

wherein R^1 to R^4 are defined as in claim 1, the tautomers, the stereoisomers, the mixtures thereof, the prodrugs thereof and the salts thereof, which have valuable pharmacological properties, particularly an inhibitory effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV).